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The Road to Commercialization of Transgenic Products in Taiwan –A Bridge Too Far

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ABSTRACT

The government of Taiwan commenced a national effort of investing in biotechnology very early in the 1980s and steadily increased public investment in various national initiatives and programs. Today, after 10 years of the National Science and Technology Program for Agricultural Biotechnology (NSTP/AB), it has established a solid research foundation, yet has achieved no notable successes in its goals of commercialization. While no one has any doubts over the technological capacity that Taiwan possesses, there are clearly gaps yet to be identified that are preventing the access of bridging R&D and markets. This paper discusses strategies in product development cycles and possible deficiencies that Taiwan must overcome to realize this great potential.

Key words: Agricultural biotechnology; Industrialization platform; Genetically modified organisms (GMOs); Regulatory science; Capacity building.

INTRODUCTION

Since 1982, the government of Taiwan has consistently promoted biotechnology and invested heavily in research and development (R&D), human capital, and infrastructure necessary to build the industry in Taiwan. By 2004, investment reached US$1.6 billion of public funds, with $35 million (2.27%) for agricultural biotechnology. These efforts over the past two decades, however, have produced few successes. Even less investment and output were observed within the private sector

To study the problem, a special project was commissioned in 2005 by the Science & Technology Policy Research and Information Center (STPI), National Applied Research Laboratories. The STPI reported its findings in 2006 in the publication, *Strategic Planning on the Development of the Taiwan Agricultural Biotechnology Industry*, in which a new strategy (hereafter referred to as the STPI model) modeled on product development cycles used in the biotech industry was identified and applied to bridge the gap in the path from R&D to commercialization.

The STPI model proposes a strategy whereby the government focuses on scarce public resources by creating an "industrialization platform" to aid in product development. The proposal was subsequently adopted and implemented by the National Science and Technology Program for Agricultural Biotechnology (NSTP/AB) as a new national strategy for Taiwan (STPI, 2006).

The STPI model was developed from the successful experiences of the biotech industry in the US (Fig. 1A, and see Appendix, Table 3, for more details). The industrialization platform identifies both early product development and advanced development phases as missing links which Taiwan needs for future R&D to succeed.

This strategy seems reasonable when one considers that all of the transgenic products in the pipeline that have been developed in Taiwan remain at the 'proof of concept' phase or earlier.

There are problems with such a view. Although it is extremely helpful for identifying the product development cycle by learning from successes of the biotech industry, currently there is no industry-wide consensus, or even nomenclature, for describing, comparing, or evaluating product development cycles in agricultural biotechnology. McElroy (2004) suggested that a standard nomenclature for describing the steps in agrobiotech product development cycles would enable better valuation of products during the commercialization process (Fig. 1B).

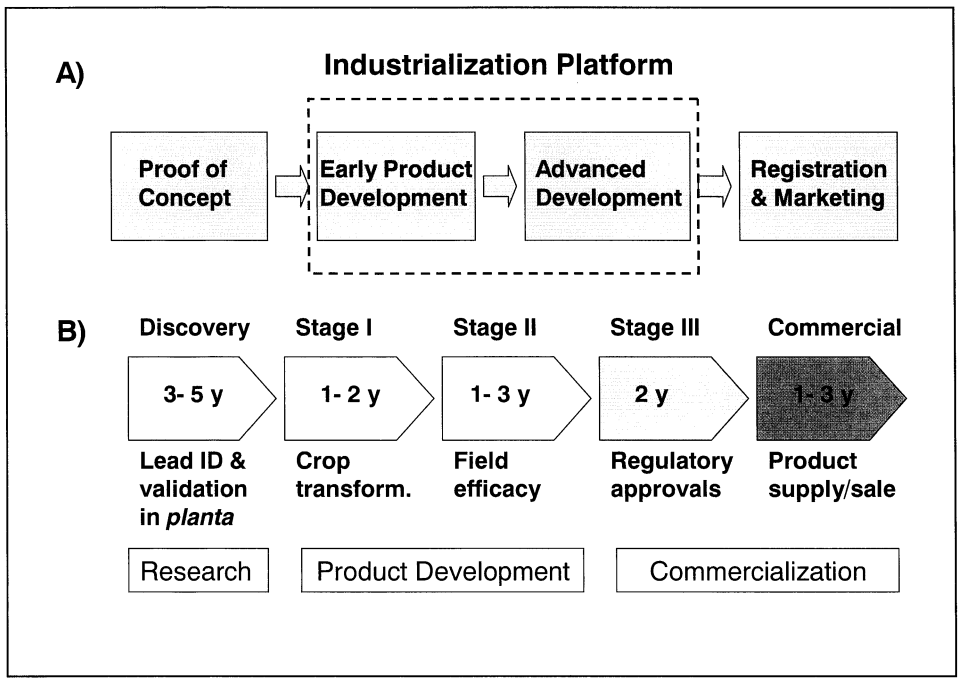

Figure 1. Product developm3ent cycle in agricultural biotechnology.
A) STPI Model; B) McElroy Model.

While the new industrialization platform may be useful for building the necessary infrastructure for traditional products, the STPI model falls short for transgenic products (i.e., genetically modified organisms; GMOs) that need to pass through the heavily regulated phase of registration (Fig. 1A) to obtain regulatory approval at stage III in the McElroy model (Fig. 1B).

The industrialization platform -- equivalent to stages I and II in the McElroy model – is an area that is much less clearly defined by industry in the product development cycle among companies with diverse experiences. Most companies, however, would agree that the bottleneck in the product development cycle to market and the most costly stage really lie beyond the industrialization platform, in particular in stage III, where regulatory approval decides whether a product may legally be placed on the market.

The task at stage III is to register the product with the authorities to obtain regulatory approval to enter the market. The requirements for registration are often for biosafety evaluations – to protect plant, animal, and human health when products are placed on the market and released into the environment. The compliance costs for biosafety at stage III are very high and vary according to the market location, in that each country has different standards for biosafety dictated by their laws and regulations. In recent years, biosafety compliance has become the critical path to gaining market access. This is especially true of GMO products where biosafety is of great concern to the public and thus heavily regulated worldwide.

The Costly Registration Stage

Biosafety requires that all biotech products be submitted to a battery of tests and regulatory scrutiny prior to commercialization. Regulatory reviews and approvals for the cultivation and food/feed consumption are country-specific. Therefore, developers must decide very early in which country's markets they will seek regulatory approval for their products. The compliance costs for producing safety data for Japan may differ greatly from that for China, or for the European Community. It has been estimated that it may currently cost multinational companies, with a global market in mind, from $5~10 million to $20~30 million per transgenic crop product (McElroy, 2003). A more-realistic study measuring the costs of biosafety regulation arrived at an estimate of $7.06~15.44 million for an insect-resistant corn (Table 1) and $6.18~14.610 million for an herbicide-resistant corn (Kalaitzandonakes *et al.*, 2006).

High regulatory costs limit the commercialization of transgenic crops to a few multinational companies. Compliance costs in stage III effectively create a barrier that blocks academic and government research institutions and small businesses from commercializing transgenic crops (PEW, 2004). It further discourages the establishment of new biotechnology firms and the flow of venture capital that finances them (McElroy, 2003).

In Taiwan, new biotech firms are growing very slowly. Government investment and outputs for research in agricultural biotechnology look disproportionate (Table 2). In the years 2002~2004, the Taiwanese government spent US$102 million to fund 1365 research projects in agrobiotech. Although the investment did produce a significant number of academic papers (932 in 3 years), it contributed little to commercialization

in terms of patents generated, the number of successful technology transfers, and new biotech companies derived from the results. After a closer look at nearly a thousand papers, we were also disappointed to find no studies were related to the science and technology of biosafety that would be needed for the stage III regulatory requirements.

Table 1. Compliance Costs for Insect-Resistant Corn, in US$1,000

Cost categories	Range of costs incurred
Preparation for hand-off of events into regulatory	20~50
Molecular characterization	300~1200
Compositional assessment	750~1500
Animal performance and safety studies	300~845
Protein production and characterization	162~1725
Toxicology (90 days in rats) – when performed	250~300
Protein safety assessment	195~ 853
Production of tissues	680~2200
Agronomic and phenotypic assessments	130~460
Non-target organism studies	100~600
ELISA development, validation, and expression analysis	415~610
EPA expenses for PIPs	150~715
EU import (detection methods and fees)	230~405
Environmental fate studies	32~800
Canada costs	40~195
Stewardship	250~1000
Facility and management overhead costs	600~4500
Total	**7060~15,440**

Table 2. Government Investment and Research Output in Agricultural Biotechnology

Year	Number of projects	US$ (x 10^6)	Papers published	Number of patents	Technology transfers	New companies
2004	423	35.1 (NT$1166)	413	0	6	0
2003	519	30.1 (NT$1000)	246	5	1	3
2002	423	36.8 (NT$1221)	273	0	4	2
Total	1365	102.0 (NT$3387)	932	5	11	5

Source: STPI, 2006.

During the period of 2001~2003, there were actual studies on the food safety of GM papaya developed by National Chung Hsing University, Taichung. The research was funded by the Council of Agriculture, and four student Master's theses were produced. Unfortunately, no results were published in peer-reviewed journals. The data were seriously flawed and grossly deficient in meeting the data requirements of the Guidance of Safety Assessment for Genetically Modified Foods published by the Department of Health (DOH). GM papaya never had a chance to complete a dossier for food safety for submission to the DOH for registration and commercial approval.

The lessons learned from the GM papaya experience were multifold. Not only are the scientists who become product developers largely unaware of the regulatory costs, but additionally, the gap between the regulatory science, practiced by industry scientists, and academic science, practiced in universities, has fundamentally been underestimated.

Industry of multinational company spends huge amounts of money on regulatory science to establish high-quality laboratories producing large amounts of data to fulfill the safety requirements demanded by regulators in order to complete product

registration. What is often not obvious to academic scientists in this field of endeavor is that much of the experimental data generated for regulatory requirements are not publishable, either for academic reasons or for business reasons of confidentiality.

The study by Kalaitzandonakes *et al.* (2006) did not take into account the large overhead costs for biotech companies. They surmised that it may cost 20% more, and prove difficult to scale up, information that has remained "business confidential" for many companies.

In 2002~2004, with the goal of commercialization, Taiwanese government investment in research reached an average of US$34 million a year. That total amount has sufficient capacity, on the scale of multinational companies, to enable several successful products worth $6~15 million each to reach the global market. So far, none has been produced. Instead of utilizing public funds in focused product development, $102 million was divided by 1365 projects where each research project got US$75,000 on average for very diverse research goals. Focus is always an issue, and while this has been criticized, there has been no resolution reached in government programs.

Since the registration process usually takes years to complete, it is necessary to maintain technical teams to respond to all newly-generated data requirements during the review process. The longer the approval process takes, the more costly it is for developers. An uncertainty with the approval process adds to the costs. Non-transparent processes in government increase the uncertainties. The speed of regulatory decision-making is an important constraint on the ability of industry to bring new products to market.

The Slow Regulatory Process

In spite of some successes over the last decade, many observers have been disappointed at the rate of development and commercialization of new biotech products in recent years. Indeed, accumulating evidence suggests that innovation and product development have slowed down, and high compliance costs for regulatory approval have been cited as a key culprit (McElroy, 2003; Bradford *et al.*, 2005; Jaffe, 2006; Kalaitzandonakes *et al.*, 2006). Over time, stage III continues to evolve, and has developed into a system with increasing sophistication in scientific methodologies and regulatory complexity.

The regulatory process of many agencies often may take years and may vary case by case. In recent years, evidence has shown that the regulatory process is getting longer and decision making is becoming slower. Some factors contributing to this slowdown in some countries may come from data sophistication that has evolved over time. Others may come from the increasing complexity of a regulatory system that is continually growing. Anti-GMO movements by NGOs and low public acceptance undoubtedly have also forced regulators all over the world to take more-precautionary measures and enact more-stringent legislative safeguards.

In the US, federal agencies engaging in product review have slowed down to more than double the length of time (Jaffe, 2006). The regulatory process for USDA in 1994~2000 took 6.1 months on average, increasing to 15.4 months in 2001~2005. The process in the FDA took 6.5 months in 1994~2000, which grew to 15.2 months in 2001~2005.

In Taiwan, the review process appears to have also slowed down in recent years. In

2001, the DOH implemented legislation to require mandatory registration of GM soybeans and corn. The first approval, Roundup Ready soybean, was completed in July 2002. By July 2006, only 12 cases had been completed for approval. In 2005, only one case completed the process, and the same so far in 2006, (Fig. 2A). The average review time took 347 days at the DOH, in contrast to 199 days for the GM soybean and corn cases processed by the USFDA (Fig. 2B).

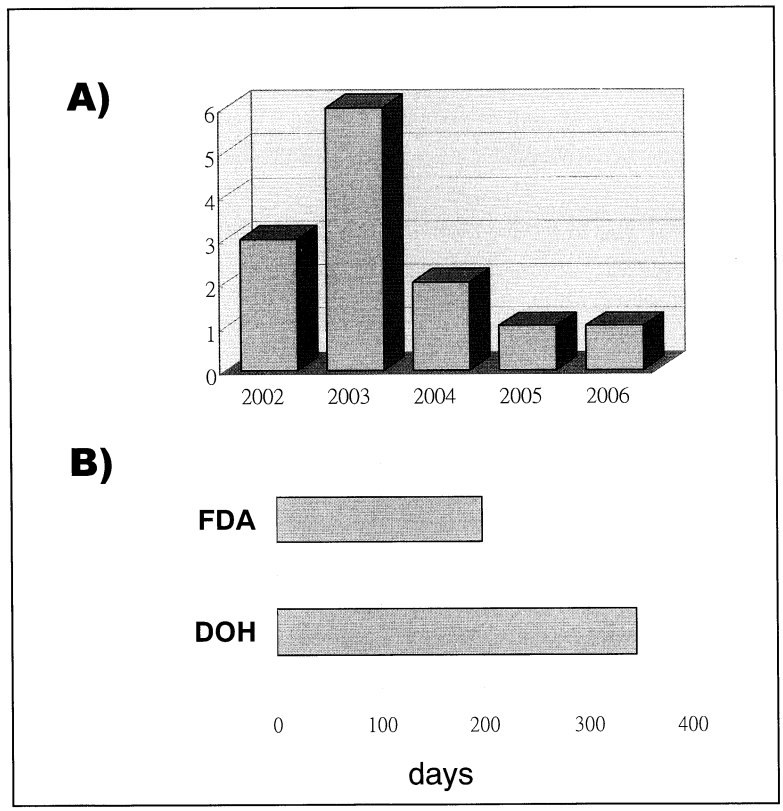

Figure 2. The regulatory process at DOH. A) Number of GM food approvals, 2002-2006. B) Comparison of approval process, in days, taken for GM soybean and GM corn at DOH and USFDA.

Despite a small portfolio of GM products covered by the current legislation (soybeans and corn), DOH has yet to develop the capacity to catch up with the number of other GM products that need to be reviewed and approved for market. In comparison to neighboring countries, for example Japan and Korea, each of which imports the same commodities from essentially the same sources as Taiwan, the DOH seriously lags behind in terms of regulatory approval of many more GM food cases that are already commercialized and are in the pipeline waiting to be processed (Fig. 3).

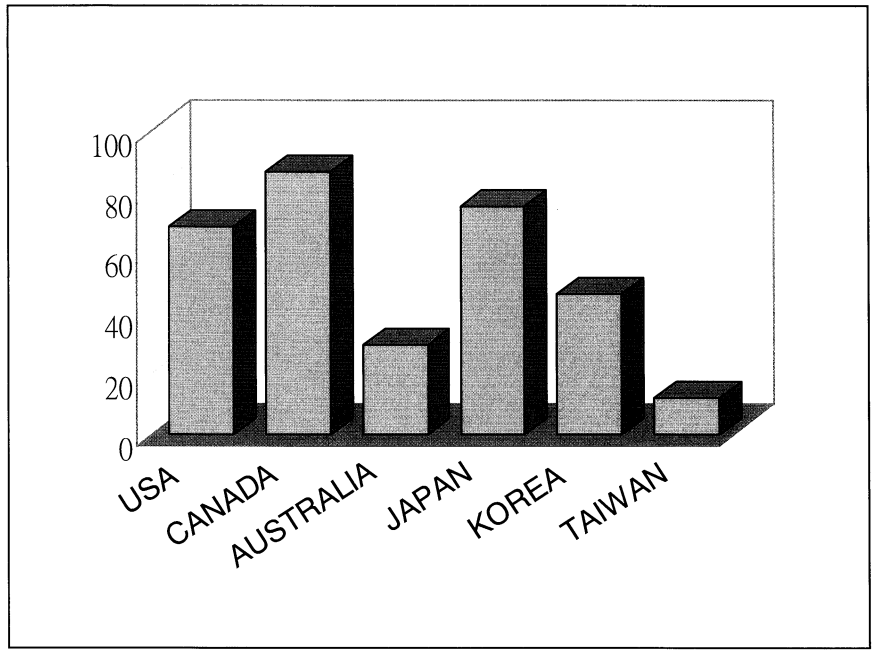

Figure 3. Number of GM Food approvals in exporting NAFTA countries and importing Asia Pacific countries (as of July 2006).

Not only is the DOH slow to catch up with this much-needed work, but the legislation itself is not ready. In November 2003, the DOH published advanced notice that it would broaden the scope of registration for all GM foods and crops. The legislation would enable domestically developed biotech products, e.g., GM papaya, GM rice, etc., to begin the approval process. Until 2006, the legislation still has not been implemented for GM products other than soybeans and corn.

Bridging the Gap – The Regulatory System

The slowdown has drawn concerns not only from industry but from foreign governments as well. Taiwan is the sixth largest agricultural market for the US and imported almost US$1 billion of US biotech products in 2005. While trade has not been interrupted, the slow approval process for new products worries the US government (USDA, 2006). In the 2006 National Trade Estimate Report on Foreign Trade Barriers, the US Trade Representative sounded the alarm "...with a number of products entering the regulatory approval pipeline and a lack of investment in a strong domestic regulatory infrastructure, delays in approvals have become more frequent." (USTR, 2006). In a comparative study of the regulatory systems in Japan and Taiwan, Chen and Watanabe (2006) observed 'pitfalls in implementing biosafety regulatory framework systems' in Taiwan and recommended that this is an urgent task for the Taiwanese government.

A 2005 survey by the Taiwan Institute of Economic Research that studied the limiting factors preventing the willingness of corporate investment in Taiwan also lists the "incompleteness of laws and regulations" as the number one factor (STPI, 2006).

Bridging the Gap – Biosafety Research

Taiwan has demonstrated great potential in developing and utilizing these technologies. Between 2002 and 2004, the Taiwanese government funded 1365 research projects in agricultural biotechnology which produced a respectable volume of academic publications, 932 papers in total (Table 2). So far, almost all the research papers produced in Taiwan are 'discovery' or stage I studies. The innovative initiative of building the "industrialization platform" will undoubtedly bring the fruits of research closer to commercialization. Those efforts do not appear to be sufficient to get past stage III of the regulatory process, and to the commercial stage where post-market compliance to various regulations plays a part.

It is important to consider the post-market commercial stage. The well-known case of StarLink, a GM corn once approved in the US, has taught everyone a good lesson. Dubious biosafety data resulted in the EPA decision to allow it for feed use but not for food use. This allowed StarLink to reach the market where it quickly made a disastrous failure, losing close to a billion dollars and resulting in many lawsuits which finally resulted in it being pulled off the market.

Since the 2001 StarLink fiasco, much progress has been made in upgrading both the technology of biosafety research and the regulations. With such a knowledge-intensive field and heavy investment, naturally, people might generally expect that the research would maximize the output of biotechnology. A study of two major science literature databases that track broad trends in plant transgenic science knowledge from 1973 to 2003 reports a similar observation (Vain, 2006). The study identified 30,624 papers, of which 14.8% were related to technology development, 71.3% were related to application of technology, and 13.8% were related to

development of genetically modified (GM) crops or feed. The expanding gap between technology development and applications may limit future transgenic science and the ability to address issues related to GM crops. Although we have not been able to analyze the nature of papers published in Taiwan in such detail, most scientists would agree that those in the category of original technology development are scarce.

The paucity of studies on technology development and on food safety/environmental risk assessment has not only hampered national efforts to commercialize GMO products to the market but has also dampened the development of science-based regulations (NRC, 2000; IOM, 2004; Bradford *et al.*, 2005; Pelletier, 2006). Above all, in order to bridge the gap from product development to commercialization, Taiwan needs studies in biosafety to fulfill the registration requirements, both locally and elsewhere in the world.

The Developing Country Model

The STPI and McElroy models are drawn from experiences in industrialized countries. In 2005, there were 21 countries in the world cultivating transgenic plants. Many of these are developing countries (James, 2005). There is much to be learned from the experiences of those developing countries.

In commercial cultivation of GM crops, India and China have far more experience at the local farmers' level, with thousands of hectares of GM crops and much accumulating knowledge and experience for future development of crop technology and associated risk management. Even Japan lags behind these Asian countries (Watanabe, 2003).

Like Japan, Taiwan has so far had no success in commercializing its own GM crops. China, however, had already succeeded in commercializing 31 products by 2000 (Rozelle *et al.*, 2001). This is not entirely surprising because developing countries, such as China and India, also invest heavily in R&D and have become the third- and fifth-ranked, respectively, behind the US, the UK and Germany, in the number of GM crop publications produced every year (Vain, 2006). The success in developing countries clearly demonstrates that R&D in these countries can and does support commercialization without the astronomical costs to achieve the same goal of reaching the market seen in industrialized nations.

While one might question that biosafety was compromised due to 'sub-standard' measures adopted in these countries, and admittedly, while much research is still needed, 10 years of global commercialization has sufficiently demonstrated that transgenic technology per se is definitely not intrinsically hazardous. Proper regulatory management within the paradigm of risk analysis could provide adequate protection to plant, animal, and human health. In that context, it is only rational to challenge the current trend which continues to move in the direction of overregulation. At the same time, there are also certain advantages to study and learn from the experiences generated by developing countries where minimal costs from public funds were used to produce many commercial products with minimal regulatory requirements, but while not necessarily compromising safety.

Like Japan, Taiwan needs regulatory agencies that have clear responsibilities, and clear, workable risk-management schemes in R&D institutions. That is especially true considering Taiwan's biotechnology R&D resources rely almost exclusively on

the public sector through such programs as the NSTP/AB. In the foreseeable future, there is little opportunity for Taiwan to build up its own private biotech companies to the scale required to compete with the biotech giants in industrial countries. Instead of building a commercial model in the pattern of the biotech giants, Taiwan has no option but to create a unique path to future agrobiotech development, perhaps taking the lead from those developing countries where small farm practices are the rule rather than the exception.

CONCLUSIONS

Ultimately, the biotechnology products grown in Taiwan are not just for domestic consumption. To survive in the global trade market, Taiwan urgently needs to build its own capacity in government by improving the domestic legislation system and in science and technology of biosafety research. The capacity for biosafety research in turn can promote policy and regulations based on sound science that would allow Taiwan to cope with the ever-evolving complex international regulatory environment.

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Appendix

Table 3. Monsanto Model of Product Development Pipeline Phases

Discovery	Phase I	Phase II	Phase III	Phase IV
Gene/Trait Identification	Proof of concept	Early development	Advanced development	Pre-launch
Average duration, 2~4 years	1~2 years	1~2 years	1~2 years	1~3 years
Average probability of success, 5%	25%	50%	75%	90%
1.High throughput screening, 2.Model crop testing	1.Gene optimization 2.Crop transformation	1.Trait development 2.Large-scale transformation 3.Pre-regulatory data	1.Trait-integration 2.Field testing 3.Regulatory data generation	1.Regulatory submission 2.Seed bulk up 3.Premarketing

Source: Fraley (2005). Available at http://www.monsanto.com/.